DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/31/2011 has been entered. Claims 12, 17-19 are cancelled. Claims 1 and 8 have been amended. Claims 1, 8-11, and 26-28, 30 are present for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 8-9, 11, 26-28 and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite a method of identifying a PTEN pathway modulating agent. The claimed method steps require the presence of an SNF1LK protein (a serine/threonine kinase) and

a test agent and detecting the effect of the agent(s) on the expression of SNF1LK. This assay is followed by a second assay that involved a cell based assay where the cell that expresses the SNF1LK is cultured in the presence of said test agent and the difference between treated verses untreated cells is determined. Furthermore the measurement is done using either a BRDU assay, cell viability assay, titrated thymidine assay, nucleosome ELISA apoptosis assay and a FOXO nuclear translocation assay. None of the steps require the presence of a PTEN.

However the specification does not clearly teach a nexus between SNF1LK and the PTEN pathway. The specification on page 2, lines 20-21 states: "Mammalian SNF1 like kinase (SNF1LK) is a serine/threonine kinase similar to Snf1 protein kinase, of *S. cerevisiae*, which is involved in the response to *"nutritional stress*". Furthermore page 5, line 5-14 of the specification teaches that SNF1LK of SEQ ID NO: 5 is a polypeptide related to MARK kinases. However the specification does not tech a link between nutritional stress, SNF1LK and PTEN.

Furthermore with regards to a FOXO nuclear localization assay, the assay comprises cells that express **MARK** (such as SNf1LK) in the presence of a test agent. However the specification does not describe any link between PTEN and SNF1LK. Moreover the last paragraph of the specification (page 41) states:

> "…Results indicated that reduced expression of SEQ ID NO: 5 (SNF1LK) led to retention of FOXO in the nucleus, similar to a reduced AKT effect. These results *suggest* involvement of MARK in the PTEN/IGF pathway."

However the specification does not provides a clear link between the PTEN pathway and the SNF1LK protein.

The essential goal of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed."

In re Barker, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). Another objective is to put the public in possession of what the applicant claims as the invention.

These claims are directed to a method of identifying an agent that modulate PTEN pathway. However specification does not describe how method steps that do not include or clearly link PTEN and the polypeptide (SNF1LK) can be used to identify a PTEN modulating agent.

The specification does not describes how structurally unrelated kinases including SEQ ID NO: 5 (considered SNF1LK), SEQ ID NO: 8 and SEQ ID NO: 10 (collectively called MARK kinases) comprising 4726 nucleotides, 1725 nucleotides or 4919 nucleotides respectively are linked to the PTEN pathway. Moreover, at the time of the instant invention the art does not teach a nexus between SEQ ID NO: 5 and the PTEN pathway.

The Federal Circuit has pointed out that under United States law, a description that does not render a claimed invention obvious cannot sufficiently describe the invention for the purposes of the written description requirement of 35 U.S.C. 112. Eli Lilly, 119 F.3d at 1567, 43 USPQ2d at 1405. Compare Fonar Corp. v. General Electric Co., 107 F.3d 1543, 1549, 41 USPQ2d 1801, 1805 (Fed. Cir. 1997).

Furthermore the specification does not describe how PTEN, a dual specificity protein phosphatase and a lipid phosphatase which dephosphorylates the phospholipid PIP_3 and thus modulates the activity of downstream signaling pathways such as activity

of AKT can be related to polynucleotides encoding SNF1LK which is similar to a "sucrose non-fermenting like kinase" which is involved in the response to nutritional stress.

In addition, the specification does not describe how the function of a defective PTEN can be overcome by expressing a recombinant polynucleotide encoding a SNF1LK polypeptide.

Given that the specification lacks description for a link between a polynucleotide encoding a SNF1LK polypeptide and PTEN pathway, the specification fails to describe the claimed invention in a clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Withdrawn -Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 8-9, 11 and 26-28 were rejected under 35 U.S.C. 102(b) as anticipated by US 2002/0025931 A1 (Meyers et al). This rejection is withdrawn following applicants argument and claim amendment.

However assuming that there is a link between PTEN and SNF1LK, based on the method steps of the claims that do not require the presence of PTEN in the assay, the following obviousness rejection would have applied.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 11 and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2002/0025931 A1 (Meyers et al) in view of Hong Sun et al (PTEN modulates cell cycle progression and cell survival by regulating phosphatidylinositol 3,4,5,-trisphosphate and Akt/protein kinase B signaling pathway. PNAS May 25, 1999 vol. 96 no. 11 6199-6204).

The method steps in claim 1, 11 and 26-28 are drawn to an assay system that uses the polynucleotide sequence of SEQ ID NO: 5 (encodes SNF1LK) or any functional fragment that encodes a polypeptide that comprises residue 27-278 of SEQ ID NO: 5 in the presence of a test agent that modulates expression of SNF1LK and following up with a second assay to determining the effect of the test agent on the activity of the SNF1LK.

In the above assay system, any agent that has an effect on the activity of the SNF1LK would be obvious over the instant claims because the assay only requires the presence of an SNF1LK polynucleotide and a test agent in to examine a test agent biased expression. This is followed by a second assay involving culturing a cell comprising an SNF1LK in the presence of a test agent to confirm the test biased activity. The result of the assay also does not require changes in expression or phosphorylation/kinase or any other effects on PTEN.

Encompassed in different embodiments, Meyers et al teach an assay that comprises SNF1LK and a test agent and also teach a cell based assay wherein a cell comprising SNF1LK is cultured in the presence of a candidate compound to examine the effect of the test compound.

The instant application does not teach a test biased effect on expression or activity of **PTEN** *per se*. The claims are drawn to a screening assay that assesses the expression level of SNF1LK in the presence of a test agent in vitro and/or in vivo cell culture and said test is followed by a second cell based assay that also measures a test agent biased activity in expression or activity of recombinant SNF1LK **not** PTEN.

Meyers et al teach a method or a "screening assay" to identify modulators, (i.e., candidate or test compounds or agents) that bind to SNF1LK (or 3 other proteins) and have a stimulatory or inhibitory effect on the expression of SNF1LK or activity of SNF1LK, or have a stimulatory or inhibitory effect on, for example, the expression or activity on a SNF1LK substrate.

Moreover, Meyers specifically teaches a cell-based assay comprising contacting a cell expressing a SNF1LK target molecule (e.g., a SNF1LK phosphorylation substrate) with a test compound and determining the ability of the test compound to modulate (e.g. stimulate or inhibit) the activity of the SNF1LK target molecule by determining the ability of the SNF1LK protein to bind to or interact with the SNF1LK target molecule, or by determining the ability of the SNF1LK protein to phosphorylate the SNF1LK target molecule.

Hong Sun et al teach that PTEN is a tumor suppressor protein that regulates the phosphatidylinositol 3, 4, 5,-trisphosphate and Akt signaling pathway and consequently modulates two critical cellular processes: cell cycle progression and cell survival. They teach that PIP_3, a product of PI_3 kinase, is an intracellular target of PTEN and suggest that PTEN acts as a

negative regulator for the PI_3-kinase/Akt signaling pathway, which controls and coordinates two major cellular processes: cell cycle progression and cell death.

Meyer also teaches that determining the activity of the target molecule can be for example, by detecting induction of a cellular second messenger of the target (e.g., intracellular Ca^{2+}, diacylglycerol, IP_3 (involved in the AKT/PTEN pathway), etc.), detecting catalytic/enzymatic activity of the target an appropriate substrate, detecting the induction of a reporter gene (comprising a target-responsive regulatory element operatively linked to a nucleic acid encoding a detectable marker, e.g., chloramphenicol acetyl transferase), or detecting a target-regulated cellular response (thus obvious over cell viability assay for example).

Meyers et al teach that SNF1LK may be involved in: 1) the regulation of transmission of signals from cellular receptors, e.g., cardiac cell growth factor receptors; 2) the modulation of the entry of cells into mitosis; 3) the modulation of cellular differentiation; 4) the modulation of cell death; and 5) the regulation of cytoskeleton function, e.g., actin bundling.

Meyers also teaches that the SNF1LK protein includes a Ser/Thr kinase site and plays a role in signaling pathways associated with cellular growth, e.g., signaling pathways associated with cell cycle regulation and differentiation.

Furthermore claim 17 in Meyer et al encompasses a method for identifying a compound capable of treating cancer or a cellular proliferation and/or differentiation disorder characterized by aberrant SNF1LK, polypeptide activity comprising assaying the ability of the compound to modulate SNF1LK nucleic acid expression or SNF1LK polypeptide activity, thereby identifying a compound capable of treating cancer or a cellular proliferation and/or

differentiation disorder characterized by aberrant SNF1LK nucleic acid expression or SNF1LK polypeptide activity.

Thus the SNF1LK in the method described by Meyer et al is a serine/threonine that is likely to be involved in the same pathway as molecules involved in the same pathway (for example PTEN which is a involved in cell cycle and cancer). Thus one of ordinary skill in the art would have been apprised that SNF1LK may be found in the same pathway as PTEN.

Given the disclosure of Meyer et al it would have been obvious to one of ordinary skill in the art to design the two step method with a reasonable expectation of success because Meyers teaches each one of the individual steps.

Thus an ordinary person skilled in the art skill would be motivated to provide the nucleic acid based assay to examine differential expression of the SNF1LK polynucleotide followed by a second assay comprising an activity based assay to provide a confirmation for any potential candidate agent(s) identified.

Furthermore, at the time of the instant invention, the art was mature with regard to the use of various assay methods and applicants were not the first to use these methods in a screening assay. For example tritiated thymidine incorporation is taught in Fig. 2 of Hong Sun et al.

With regards to claim 11, Meyers also teaches a methods of using the polynucleotide of SEQ ID NO: 1 and encoded protein to treat a subject having a disorder characterized by an aberrant expression or activity of the nucleic acid sequence of SEQ ID NO: 1 or encoded protein (this would be within a limitation of claim 11). They state that the aberrant protein or nucleic acid expression can be characterized by a cellular growth related disorder and teach that such aberrance can be treated by administering a native protein or the nucleic acid of SEQ ID NO: 1

as a modulators. Meyers eta also teach the use of host cells into which the expression vectors have been introduced, and non-human transgenic animals in which a sequence in which a functionally active form of SEQ ID NO: 5 (SEQ ID NO: 1) gene has been introduced or disrupted. Such host cells and transgenic non-human animals can be used in a diagnostic, screening, and therapeutic methods. Thus claim 11 would be obvious. Therefore claims 1, 11 and 26-28 are obvious over the teachings of Meyers et al in view of Hong Sun et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 10 was rejected under 35 U.S.C. 103(a) as being unpatentable over Meyers et al in view of Summerton et al (Morpholino antisense oligomers: the case for an RNase H-independent structural type (Biochimica et Biophysica Acta 1489 (1999) 141-158) or Stein et al (A Specificity Comparison of four antisense types: Morpholino, 2'-OMethyl RNA, DNA, and Phosphorothioate DNA. Antisense & Nucleic acid Drug Development 7:151-157 (1997).

Claim 10 in the instant application teaches that the nucleic acid modulator is a phosphothioate morpholino oligomer (PMO). Claim 30 in the instant application is drawn to a nucleic acid modulator wherein said modulator is a dsRNA or an siRNA modulator.

Furthermore claim 8, 9 and 30 (not claim 10 as correctly pointed out) were was rejected under 35 U.S.C. 103(a) as being unpatentable over Meyers et al in view of Martinez et al.

(Synthetic small inhibiting RNAs: Efficient tools to inactivate oncogenic mutations and restore p53 pathways PNAS vol. 99 no. 23 pages 14849-14854 Oct. 28, 2002). (It should be noted that claim 30 depends on claim 8 and that claim 9 recites an antisense oligomer).

Upon further consideration claims 8-10 encompass a method that use a polynucleotide comprising SEQ ID NO: 5 which is a 4726 nucleotides long. Meyer et al do not teach use of a polynucleotide of this size. The polynucleotide used by Meyer is 2969 nucleotides. Therefore these rejections are withdrawn.

Conclusion: No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KAGNEW H. GEBREYESUS whose telephone number is (571)272-2937. The examiner can normally be reached on 8:30am-5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MANJUNATH RAO can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KAGNEW H GEBREYESUS/
Primary Examiner, Art Unit 1656
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